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The Lancet Rheumatology

DOI:
https://doi.org/10.1016/S2665-9913(21)00036-9

Published: 01/05/2021

Publisher's PDF, also known as Version of record

Surgical microdiscectomy versus transforaminal epidural steroid injection in patients with sciatica secondary to herniated lumbar disc (NERVES): a phase 3, multicentre, open-label, randomised controlled trial and economic evaluation

Martin John Wilby, Ashley Best, Eifiona Wood, Girvan Burnside, Emma Bedson, Hannah Short, Dianne Wheatley, Daniel Hill-McManus, Manohar Sharma, Simon Clark, Ganesan Baranidharan, Cathy Price, Richard Mannion, Peter J Hutchinson, Dyfrig A Hughes, Anthony Marson, Paula R Williamson

Summary

Background The optimal invasive treatment for sciatica secondary to herniated lumbar disc remains controversial, with a paucity of evidence for use of non-surgical treatments such as transforaminal epidural steroid injection (TFESI) over surgical microdiscectomy. We aimed to investigate the clinical and cost-effectiveness of these options for management of radicular pain secondary to herniated lumbar disc.

Methods We did a pragmatic, multicentre, phase 3, open-label, randomised controlled trial at 11 spinal units across the UK. Eligible patients were aged 16–65 years, had MRI-confirmed non-emergency sciatica secondary to herniated lumbar disc with symptom duration between 6 weeks and 12 months, and had leg pain that was not responsive to non-invasive management. Participants were randomly assigned (1:1) to receive either TFESI or surgical microdiscectomy by an online randomisation system that was stratified by centre with random permuted blocks. The primary outcome was Oswestry Disability Questionnaire (ODQ) score at 18 weeks. All randomly assigned participants who completed a valid ODQ at baseline and at 18 weeks were included in the analysis. Safety analysis included all treated participants. Cost-effectiveness was estimated from the EuroQol-5D-5L, Hospital Episode Statistics, medication usage, and self-reported resource-use data. This trial was registered with ISRCTN, number ISRCTN04820368, and EudraCT, number 2014-002751-25.

Findings Between March 6, 2015, and Dec 21, 2017, 163 (15%) of 1055 screened patients were enrolled, with 80 participants (49%) randomly assigned to the TFESI group and 83 participants (51%) to the surgery group. At week 18, ODQ scores were 30·02 (SD 24·38) for 63 assessed patients in the TFESI group and 22·30 (19·83) for 61 assessed patients in the surgery group. Mean improvement was 24·52 points (18·89) for the TFESI group and 26·74 points (21·35) for the surgery group, with an estimated treatment difference of –4·25 (95% CI –11·09 to 2·59; p=0·22). There were four serious adverse events in four participants associated with surgery, and none with TFESI. Compared with TFESI, surgery had an incremental cost-effectiveness ratio of £38 737 per quality-adjusted life-year gained, and a 0·17 probability of being cost-effective at a willingness-to-pay threshold of £20 000 per quality-adjusted life-year.

Interpretation For patients with sciatica secondary to herniated lumbar disc, with symptom duration of up to 12 months, TFESI should be considered as a first invasive treatment option. Surgery is unlikely to be a cost-effective alternative to TFESI.

Funding Health Technology Assessment programme of the National Institute for Health Research (NIHR), UK.

Introduction

Herniated lumbar disc resulting in back and leg pain travelling below the knee, sciatica, or radiculopathy is a worldwide burden to society.[1] The condition affects an estimated 11% of patients presenting to their primary-care provider worldwide, with an annual prevalence estimated to be 2·2%.[2,3] Generally, outcomes are favourable and 80% of patients improve with conservative care within 12–24 months.[4] However, given that patients affected by this condition are typically aged 40–45 years, there is a risk of loss of livelihood if it is not managed promptly.[2,3]

Treatment options have been considered by various expert-led guidelines,[5–7] but no consensus exists for transforaminal epidural steroid injection (TFESI) due to a scarcity of class I evidence. Generally, once analgesia

Lancet Rheumatol 2021; 3: e347–56

Published Online March 18, 2021 https://doi.org/10.1016/S2665-9913(21)00036-9

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Research in context

Evidence before this study

There is considerable uncertainty about the clinical effectiveness of epidurals in sciatica compared with surgery for treatment of herniated lumbar disc. However, transforaminal epidural steroid injection (TFESI), a newer and more precise treatment option, offered promise given that it can deliver the drug in a closer proximity to the site of pathology. We searched PubMed using the term "sciatica epidural steroid" immediately before the initial development of the NERVES protocol in 2013–14 and found that previous evidence supporting TFESI had come from cohort studies or single-centre studies, without clear specification of the non-surgical treatments provided. A meta-analysis from 2015 suggested that non-opioid analgesia, TFESI, and surgery were effective management options for sciatica secondary to uncomplicated herniated lumbar disc. However, the effectiveness of TFESI compared with surgery for herniated lumbar disc was uncertain, leading to wide variation in management guidelines for this common condition.

Added value of this study

NERVES is the first multicentre randomised trial directly comparing surgical microdiscectomy with TFESI on a 1:1 allocation basis as initial invasive treatment for sciatica secondary to herniated lumbar disc. There was no significant difference between TFESI and surgery pathways in clinical outcome, and surgery is unlikely to be a cost-effective alternative to TFESI. Complications of surgery were significant, offsetting any benefits of surgery as an early treatment, whereas only minor adverse events were seen with TFESI.

Implications of all the available evidence

NERVES provides high-quality evidence for a stepwise treatment framework of uncomplicated sciatica secondary to herniated lumbar disc with symptom duration of up to 12 months. TFESI would be less costly as an initial alternative to surgery for this condition, while achieving similar levels of improved outcomes.

and lifestyle-modifying treatments have failed, steroid nerve root injections and surgical microdiscectomy are recommended for severe persistent cases. Stepwise care approaches based on treatment with non-opioids have been identified as likely to represent a more cost-effective approach than strategies involving direct referral for disc surgery;[8] however, evidence for a stepwise treatment progression involving TFESI is scarce. Following various randomised trials comparing surgical treatments with non-surgical therapy,[9–12] surgery is often deemed the most successful treatment option, leading to more than 10 000 discectomy procedures per year in the UK and 190 000 such procedures in the USA.[13] The costs to the UK's National Health Service (NHS) for microdiscectomy (requiring patients to be hospitalised for 2 nights, on average) are approximately £4500 compared with £700 for TFESI.[14]

A single-centre randomised trial of 128 patients compared surgery with conservative care (including steroid injections) for sciatica secondary to herniated lumbar disc and found that surgery provided better clinical improvement in leg pain scores by 24 points.[15] Although this study reported a surgical benefit, there was a clear difference in safety profiles between treatments, with nine adverse events (including one nerve root injury) in patients receiving surgery and none in patients managed conservatively. Furthermore, a single-institution study might not be generalisable across wider health-care providers. Although treatment for radiculopathy with TFESI offers theoretical cost advantages and reduced risk compared with surgery, robust class I clinical data supporting its efficacy are scarce,[8,16] and there is no worldwide consensus on the use of TFESI.[3] We are aware of only one other trial comparing the direct effect of surgery with that of epidural steroid injections in 100 patients with sciatica secondary to lumbar disc herniation.[17] However, this trial was also a single-centre study and the route of administration was via a posterior interlaminar (lumbar puncture) injection, as opposed to TFESI. The trial showed that steroid injections avoided the need for surgery in 23 (46%) of 50 patients.[17] In view of conflicting clinical evidence, we aimed to complete the first multicentre, randomised controlled trial comparing the clinical effectiveness of TFESI with that of surgical microdiscectomy for management of radicular pain secondary to herniated lumbar disc in patients with non-emergency presentation of sciatica with symptom duration of up to 12 months. We also aimed to assess cost-effectiveness and quality of life outcomes of both treatments.

See Online for appendix

Methods

Study design

NERVES is a pragmatic, multicentre, phase 3, randomised controlled trial, with an internal pilot phase, comparing surgical microdiscectomy with TFESI in patients with sciatica secondary to herniated lumbar disc with symptom duration of up to 12 months. Participants were recruited from and followed up at 11 spinal tertiary units (outpatient neurosurgical, pain, and orthopaedic clinics; appendix pp 2–3) across the UK. The initial plan was to limit duration of symptoms at screening to 6 months. However, this criterion had a negative impact on recruitment because few patients were receiving specialist treatment within the NHS by this time, so the protocol was extended to 1 year of symptoms. The main aim of treatment was to relieve sciatica symptoms in patients as quickly and safely as possible.

An independent trial steering committee viewed reports with treatment assignment concealed, and an independent

data monitoring committee viewed unmasked reports regularly to assess conduct and progress, including safety.

The trial was granted Clinical Trial Authorisation (reference 21322/004/001) by the Medicines and Healthcare products Regulatory Agency. The trial protocol was also approved by a research ethics committee (National Research Ethics Service Committee North West–Liverpool Central; reference 14/NW/1219) and has been published.[18]

Participants

All participants required an MRI diagnosis of nerve compression secondary to herniated lumbar disc and had leg pain that was non-responsive to at least one attempt of conservative, non-invasive management. A screening log was maintained at each trial centre, with information on eligibility, consent, and randomisation. Eligible participants were aged 16–65 years, had clinical evaluation of leg pain by a consultant spinal surgeon that was deemed concordant with nerve compression seen on MRI, and had a duration of symptoms between 6 weeks and 12 months. Patients with emergency cases of significant ankle weakness or threatened cauda equina syndrome were excluded, as were those with far lateral disc prolapses. A full list of inclusion and exclusion criteria is in the appendix (p 2). Eligible participants provided written informed consent before participating in the trial.

Randomisation and masking

Participants were randomly assigned (1:1) to receive either TFESI or surgical microdiscectomy (surgery) with an online randomisation system. A designated member of the site team, usually a clinician or nurse involved in the participant's care, did the online randomisation. Randomisation was stratified by centre and used permuted blocks of random variable length (block sizes two and four). The randomisation sequence was generated by an independent statistician, and allocations were concealed from investigators and participants before recruitment. It was not possible to mask investigators and participants due to the treatments received.

Procedures

Surgery for posterolateral herniated lumbar disc was done following a standard open surgical microdiscectomy technique with an operative microscope, delivered by a consultant spinal surgeon. Specialists identified the correct side and level before treatment with level localisation using an image intensifier. The nature of disc prolapse (eg, contained, extruded, or sequestrated) was recorded by the operating surgeon, along with spinal level.

TFESI was completed by pain specialists, radiologists, or spinal surgeons as per local policy or technique with the lateral foraminal portal of entry. All fluoroscopically guided techniques were permitted to specify the correct level. Radiological level and appropriate spread of contrast were confirmed by the operator. To minimise variability across participating centres, the recommended injection regimen was 20–60 mg triamcinolone acetonide and 2 mL of 0·25% levobupivacaine. A second injection of the same dose was permitted if the injection was considered partially effective.

For both groups, treatment was recommended within 6 weeks of randomisation. Participants were allowed to crossover and subsequently receive the non-allocated treatment if primary treatment was considered ineffective. Participants were followed up for 54–62 weeks. Questionnaires were collected at 18, 30, 42, and 54 weeks, each within a window of 2 weeks. All questionnaires were completed at hospital visits, except for those at 30 and 42 weeks, which were delivered by post. The types of data and collection methods are detailed in the study protocol.[18]

An assessment of related adverse events was done at each study clinic visit at 18 weeks and 54 weeks after treatment. All related serious adverse events were reported within 24 h of site awareness of event. Related adverse events and serious adverse events were reported throughout the trial follow-up period.

Outcomes

The primary outcome was patient-reported Oswestry Disability Questionnaire (ODQ) score (range 0–100) at 18 weeks after randomisation.[19] Secondary outcomes were ODQ score at weeks 30, 42, and 54;[19] numerical rating scores (range 0–100) for leg pain and back pain, two-item Likert Scale (range 1–5) to assess patient treatment satisfaction,[20] Modified Roland-Morris (MRM) outcome score (range 0–24) for sciatica,[21] and Core Outcome Measures Index (COMI) score (range 0–10)[20] at weeks 18, 30, 42, and 54; work status (eg, return to work and work days lost, if applicable); and cost-effectiveness, expressed as incremental cost per quality-adjusted life-year (QALY) gained, assessed with EuroQol 5D-5L.

Statistical analysis

To detect a clinically important difference of 10 points on the ODQ at a 5% significance level with 90% power, a total of 172 participants were required. The choice of 10 points is based on widely accepted practice, and is at the lower end of the range of differences recommended in a study specifically addressing the issue.[22] We assumed an SD of 20 points on the basis of a similar population in UK-based trials.[23] The initial target sample size for the trial was 200, which would allow for a 10% rate of missing outcome data. Because this initial sample size calculation did not account for the analysis being adjusted for baseline values of ODQ, and because recruitment targets were not being met, the sample size was recalculated after outcome data was received for 47 participants. A masked analysis of correlation between baseline and follow-up ODQ scores was done to adjust the sample size calculation. Based on the observed correlation of 0·49, the revised sample size to achieve 90% power was 66 participants per group, which was increased to 74 participants per group (148 in total) to allow for 10% loss to follow-up.

Analyses followed a prespecified statistical analysis plan. The primary outcome (ODQ score at 18 weeks after randomisation) was compared between groups with a linear regression model, adjusted for baseline ODQ, with centre as a random effect. ODQ score, visual analogue scores (VAS) for back pain, VAS for leg pain, MRM outcome score, and COMI score at all follow-up visits were analysed with a repeated measures mixed-effects model adjusting for baseline outcome measure, treatment group, time (as a continuous variable), and a time-treatment arm interaction (if significant). Centre and participant were random effects in the repeated measures models. A second model adjusted for other prespecified variables, age, sex, duration of symptoms, body-mass index, and size of disc prolapse (as a percentage of the diameter of the spinal canal, categorised as <25%, 25–50%, or >50%). The Likert scale for satisfaction with care was analysed with the Mann-Whitney *U* test. Employment status was analysed with a χ^2 test. The intention-to-treat principle was applied as far as was possible (ie, where data were available). The analysis set for the primary outcome included all participants with a valid ODQ score (≥8 of 10 items) at baseline and at 18 weeks (range 12–24 weeks) after randomisation. The safety analysis was done in all participants who were treated and received at least one surgery or TFESI.

A sensitivity analysis was done with multiple imputation to assess the robustness of the analysis to missing primary outcome data (appendix pp 36–37).

A post-hoc analysis was done with joint modelling of the longitudinal outcomes (ie, ODQ scores, VAS back pain, VAS leg pain, MRM scores, and COMI scores) and the time to study dropout for each outcome to address the possibility of informative dropout (appendix p 37).

All analyses were done using SAS Software (version 9.4), with the exception of the joint modelling analyses, which used the joineR package in R.[24]

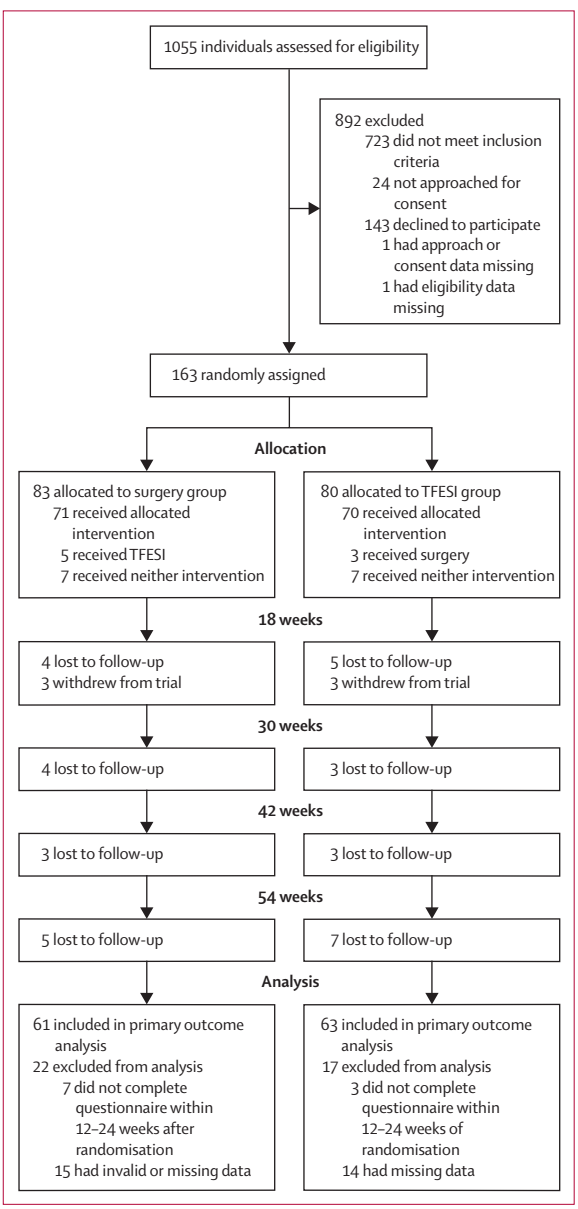

Figure 1: **Trial profile**
TFESI=transforaminal epidural steroid injection.

Economic analysis

The economic analysis was done over the 54 week trial period and adopted the perspective of the NHS in England, UK (appendix pp 12–33). Within-trial resource use was obtained from routine NHS Hospital Episode Statistics patient-level data, trial case report forms, and patient-completed questionnaires. Patient questionnaires were administered at baseline and treatment visits, and at approximately weeks 18, 30, 42, and 54 after baseline. Unit costs were obtained from standard sources,[14,25,26] valued in sterling, and based on 2017–18 prices with inflation indices applied as necessary (appendix pp 12–17). Utilities were estimated from responses to the EuroQol 5D-5L multi-attribute utility instrument and applying the 3L mapping algorithm.[27] Treatment costs were applied on the basis of treatment received.

When data were missing for utilities at baseline, weeks 18 or 54, or for any patient-completed resource use cost data, completed datasets were generated via multiple imputation before analysis. QALYs were modelled using linear regression, and total costs using a generalised linear model with a log-link function and gamma probability distribution. The QALY model included covariates for treatment allocation and baseline utility, and the model for total costs included covariates for treatment allocation and baseline costs.

The primary outcome of the economic evaluation was the incremental cost per QALY of surgery compared with that of TFESI. Uncertainties in economic outcomes were analysed using non-parametric bootstrapping, with

10 000 replications of the patient-level data, and presented as probabilities of cost-effectiveness at threshold levels of willingness to pay. Methods for the base-case analysis are presented in the appendix (pp 20–21). Scenario analyses comprised inclusion of participants with complete datasets only, out-of-pocket costs and productivity losses arising from time off work that approximated a societal perspective, alternative QALY valuation methods, the effect of varying the doses of as-needed medications, and considering only sciatica-related costs.

This trial was registered with ISRCTN, number ISRCTN04820368, and EudraCT, number 2014-002751-25.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 6, 2015, and Dec 21, 2017, we assessed 1055 patients for eligibility and recruited 163 participants from 11 centres (figure 1, table 1). The trial stopped when all participants had completed follow-up. 80 participants (49%) were randomly assigned to the TFESI group and 83 participants (51%) to the surgery group (figure 1; appendix pp 2–5). Mean length of symptom duration at time of treatment for patients who received treatment during the trial was 26·8 weeks. The majority of prolapses (92 [56%] of 163) occurred at L5–S1. Most operated cases (53 [72%] of 74) were for contained disc prolapses. Almost all cases (98 [93%] of 105) were operated directly by consultant spinal surgeons, with the remainder being done by senior trainees under direct consultant supervision.

Some participants did not receive the allocated treatment. Of the 83 patients randomly assigned to the surgery group, seven (8%) received TFESI only and four (5%) received neither treatment during the trial (appendix p 6). Of the 80 patients randomly assigned to the TFESI group, five (6%) received surgery only and four (5%) received neither treatment (appendix p 6).

During the trial, 28 patients (35%) allocated to the TFESI group received both trial treatments, and four patients (5%) allocated to the surgery group received both interventions (appendix p 6). Seven patients overall (4%; two in the TFESI group and five in the surgery group) received a second TFESI injection during the study, at times ranging from the same day as the first injection to 235 days later.

63 (79%) of 80 patients randomly assigned to the TFESI group and 61 (73%) of 83 patients in the surgery group were included in the primary outcome analysis. Both groups showed similar improvements in ODQ scores from baseline to week 18 (table 2). A post-hoc classification showed that a similar proportion of participants in both groups achieved an improvement of 10 points or more on the ODQ. Only eight participants (13%) in the surgery group and six (10%) in the TFESI group showed deterioration in symptoms.

	Surgery group (n=83)	TFESI group (n=80)
Sex		
Female	46 (55%)	40 (50%)
Male	37 (45%)	40 (50%)
Age, years	43·5 (9·9)	41·2 (8·6)
Body-mass index, kg/m²	28·2 (5·3)*	27·2 (6·4)†
Weeks with symptoms	21·5 (10·7)	21·1 (11·2)
Currently employed‡		
No	21 (25%)	13 (16%)
Yes	62 (75%)	66 (84%)
Not able to work	41 (66%)	34 (52%)
Able to work	21 (34%)	32 (48%)

Data are n (%) or mean (SD). TFESI=transforaminal epidural steroid injection. *Data available for 74 participants. †Data available for 68 participants. ‡Data available for 83 patients in the surgery group and 79 participants in the TFESI group.

Table 1: **Baseline characteristics**

ODQ scores did not differ between groups at week 18, with the model effect estimate of surgery versus TFESI being –4·25 (95% CI –11·09 to 2·59; p=0·22). From this model, we estimate that surgery would result in an average improvement in ODQ score of 4·25 points more than would TFESI, which is less than the minimum clinically important difference of 10 points. Figure 2 presents the distribution of ODQ score improvements at the primary outcome timepoint of 18 weeks after randomisation.

Of the 61 patients randomly assigned to the surgery group and who were included in the primary analysis, two (3%) also received TFESI before completing the questionnaire at week 18. In the TFESI group, 13 (21%) of 63 participants with valid primary outcome data received surgery after receiving TFESI.

The second model, adjusting for additional covariates, gave an effect estimate of surgery versus TFESI of –5·03 (–12·76 to 2·70). An additional variable, level of disc prolapse, was included in a post-hoc analysis. This model resulted in an estimate of –4·94 (–12·81 to 2·93).

Because more than 10% of data was missing (39 [24%] of 163 participants) for the primary outcome, a sensitivity analysis was done using multiple imputation. The effect estimate of surgery versus TFESI from the imputation analysis was –3·08 (–10·16 to 3·99). A post-hoc sensitivity analysis was done using multiple imputation, but only using baseline ODQ to impute a score for week 18. The effect estimate of surgery versus TFESI from the post-hoc imputation analysis was –3·26 (–9·91 to 3·39). The assumption of missing at random was explored with pattern mixture modelling and did not change conclusions. Additional details on the imputation are in the appendix (pp 36–37).

ODQ scores at week 18 in the longitudinal model improved by 27·2 points in the surgery group, compared

	Surgery group	TFESI group	Total
ODQ score at baseline*	49·39 (17·81)	53·74 (19·35)	51·51 (18·64)
ODQ score at week 18†	22·30 (19·83)	30·02 (24·38)	26·22 (22·51)
Difference in ODQ scores (SD; 95% CI)†	–26·74 (21·35; –32·21 to –21·27)	–24·52 (18·89; –29·28 to –19·76)	–25·61 (20·09; –29·18 to –22·04)
Difference category (post-hoc)			
≥10 point improvement	45 (74%)	43 (68%)	88 (71%)
<10 point improvement	8 (13%)	14 (22%)	22 (18%)
Deterioration in symptoms	8 (13%)	6 (10%)	14 (11%)

Data are mean (SD) or n (%), unless otherwise indicated. TFESI=transforaminal epidural steroid injection. ODQ=Oswestry Disability Questionnaire. *Data available for 83 participants in the surgery group and 79 participants in the TFESI group. †Data available for 61 participants in the surgery group and 63 participants in the TFESI group.

Table 2: **Summary of ODQ scores at baseline and at week 18**

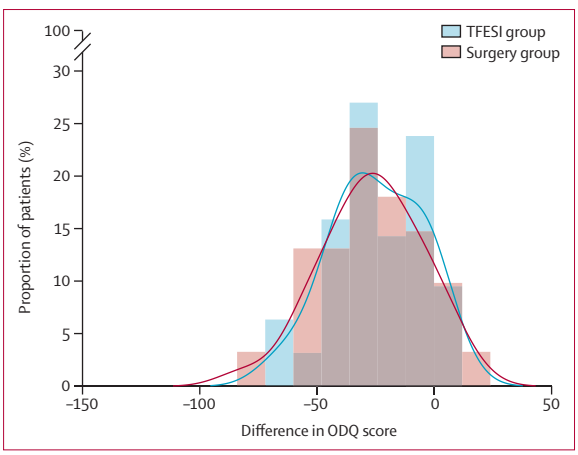

Figure 2: **Distribution of differences in ODQ scores between baseline and week 18**

Fitted lines are kernel density estimates; histogram show percentage of patients in nine bins. TFESI=transforaminal epidural steroid injection. ODQ=Oswestry Disability Questionnaire.

with 24·3 points in the TFESI group (appendix pp 10–11). The adjusted estimate for the average effect of surgery versus TFESI over all timepoints was –4·67 (–10·61 to 1·28; p=0·12). For the joint modelling post-hoc analysis of ODQ scores, the adjusted effect estimate of surgery versus TFESI was –4·62 (–9·84 to 1·27; p=0·11; appendix p 37).

Leg pain VAS scores at week 18 improved by 58·3 points in the surgery group, compared with 43·6 points in the TFESI group (appendix pp 10–11). The adjusted estimate for the average effect of surgery versus TFESI over all timepoints was –7·04 (–15·81 to 1·73; p=0·11). For the joint modelling post-hoc analysis of VAS leg pain scores, the adjusted effect estimate of surgery versus TFESI was –7·06 (–15·82 to 0·86; p=0·098; appendix p 37).

Back pain VAS scores at week 18 improved by 26·0 points in the surgery group, compared with 23·4 points in the TFESI group (appendix pp 10–11). The adjusted effect estimate of surgery versus TFESI was –3·01 (–11·29 to 5·26; p=0·47). For the joint modelling post-hoc analysis of VAS back pain scores, the adjusted effect estimate of surgery versus TFESI was –2·87 (–10·58 to 3·16; p=0·46; appendix p 37).

MRM scores at week 18 improved by 9·1 points in the surgery group, compared with 7·7 points in the TFESI group (appendix pp 10–11). The adjusted effect estimate of surgery versus TFESI was –1·82 (–3·67 to 0·03; p=0·054). For the joint modelling post-hoc analysis of MRM scores, the adjusted effect estimate of surgery versus TFESI was –1·72 (–3·44 to 0·10; p=0·063; appendix p 37).

COMI scores at week 18 improved by 3·9 points in the surgery group, compared with 3·1 points in the TFESI group (appendix pp 10–11). The adjusted effect estimate of surgery versus TFESI was –0·77 (–1·58 to 0·03; p=0·059). For the joint modelling post-hoc analysis of COMI scores, the adjusted effect estimate of surgery versus TFESI was –0·78 (–1·54 to –0·02; p=0·046; appendix p 37). The estimate for surgery versus TFESI is similar to the longitudinal mixed model; however, 95% CIs suggest a significant treatment effect once adjusted for informative dropout, although this is less than the minimal clinically important difference of 2·2.[28]

No participants died during the study period. There were 26 adverse events, 18 events in 15 participants who had surgery and eight events in three participants who had TFESI (table 3). There were four serious adverse events in four participants, all associated with surgery (appendix pp 34–35). None of the serious adverse events were unexpected. One (1%) of the 105 participants who ended up having surgery developed a clinically significant nerve palsy (ie, foot drop).

Data for 157 participants were included in the economic evaluation (80 in the surgery group and 77 in the TFESI group). Six participants who withdrew early on were excluded because neither outcome nor Hospital Episode Statistics data were available. Some data were missing for costs and EuroQol 5D-5L, in particular the postal questionnaires at weeks 30 and 42 (appendix p 22). Observed participants' use of health-care resources were similar at baseline for the 3 months before randomisation (appendix pp 23–24). Observed use of resources in primary and secondary care during the 54 week trial period are reported in the appendix (pp 24–25). The corresponding NHS costs were higher for surgery at £6683 (95% CI £5632–8074) than for TFESI at £4422 (£3682–5291), with a difference of £2261 (£706–3589; table 4; appendix pp 25–26), mainly due to cost differences in admitted patient care.

Utility scores were similar between groups at baseline (appendix p 27). At 54 weeks, mean observed utility was 0·718 (0·649 to 0·784) for the surgery group and 0·659 (0·573 to 0·739) for the TFESI group. There was no evidence of a significant difference in QALYs over the 54 week trial duration (difference 0·062 [–0·033 to 0·155]; table 4; appendix pp 27–28).

The base-case analysis with imputation for missing data, regression analysis, and non-parametric bootstrapping

	Surgery group (n=105)		TFESI group (n=82)		Total (n=155)	
	Number of events	Number of participants (%)	Number of events	Number of participants (%)	Number of events	Number of participants (%)
Total	18	15 (14%)	8	3 (4%)	26	18 (12%)
Nervous system disorders						
Hypoaesthesia	1	1 (1%)	5	2 (2%)	6	3 (2%)
Cerebrospinal fluid leakage	1	1 (1%)	0	0 (0%)	1	1 (1%)
Peroneal nerve palsy	1	1 (1%)	0	0 (0%)	1	1 (1%)
Radicular pain	1	1 (1%)	0	0 (0%)	1	1 (1%)
Injury, poisoning, and procedural complications						
Dural tear	4	4 (4%)	0	0 (0%)	4	4 (3%)
Pseudomeningocele	2	2 (2%)	0	0 (0%)	2	2 (1%)
Surgical procedure repeated	1	1 (1%)	0	0 (0%)	1	1 (1%)
Wound complication	1	1 (1%)	0	0 (0%)	1	1 (1%)
Infections and infestations						
Post-operative wound infection	2	2 (2%)	0	0 (0%)	2	2 (1%)
Wound infection	1	1 (1%)	0	0 (0%)	1	1 (1%)
Musculoskeletal and connective tissue disorders						
Pain in extremity*	1	1 (1%)	1	1 (1%)	2	2 (1%)
Sciatica	1	1 (1%)	0	0 (0%)	1	1 (1%)
Renal and urinary disorders						
Pollakiuria	0	0	1	1 (1%)	1	1 (1%)
Urinary incontinence	0	0	1	1 (1%)	1	1 (1%)
General disorders and administration site conditions						
Swelling	1	1 (1%)	0	0 (0%)	1	1 (1%)

Adverse events are reported by treatment received rather than by allocated treatment. TFESI=transforaminal epidural steroid injection. *Refers to leg pain.

Table 3: **Adverse events**

yielded total costs of £6919 (£5503 to £8046) and total QALYs of 0·616 (0·570 to 0·671) for surgery, and total costs of £4706 (£3821 to £5516) and total QALYs of 0·559 (0·503 to 0·620) for TFESI. Incremental costs of £2212 (£629 to £3677) and QALYs of 0·057 (–0·009 to 0·124) resulted in an incremental cost-effectiveness ratio of £38737 per QALY gained and a 0·17 probability of surgery being cost-effective at a willingness-to-pay threshold of £20000 per QALY (table 4; appendix pp 28–29).

None of the scenario analyses that used imputed datasets resulted in incremental cost-effectiveness ratios below the £20000 per QALY gained threshold (appendix p 31).

Discussion

To our knowledge, NERVES is the first randomised trial to directly compare surgical microdiscectomy with TFESI as initial invasive treatments for management of radicular pain secondary to herniated lumbar disc in patients with non-emergency presentation of sciatica with symptom duration of up to 12 months. No significant differences were found for primary or secondary outcomes, with 47 (59%) of the 80 patients in the TFESI group not receiving surgery. This study was a pragmatic trial done within the NHS, recruiting patients whose symptoms had not improved within 6 weeks of conservative management and required additional treatment. Given the National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold of £20000 per QALY, and that our results reported an incremental cost-effectiveness ratio of £38737 per QALY gained, it is unlikely that surgery as a first invasive treatment would be considered a cost-effective use of NHS resources, compared with TFESI. Our findings were robust to several modelling scenarios and assumptions, and indicated that incremental QALY gains did not justify the increased costs of surgery.

Previous studies of sciatica comparing surgery with conservative management have reported surgery to be more effective than non-operative management. A 2020 study with a similar cohort to NERVES showed that surgery was superior to non-operative management in patients with sciatica of up to 12 months duration, with leg pain improvements greater than 20 points following surgery.[15] The primary outcome of the study was leg pain; however, because the trial was limited to one health-care institution, it might not be generalisable across wider populations. Although we found that surgery resulted in greater improvements in leg pain than did TFESI, this effect was limited to 7 of 100 VAS points.

The NERVES trial has methodological strengths: it was multicentred (11 units) across a single country and the treatment policy for the non-surgical group was clearly

	Surgery group	TFESI group	Mean difference
Observed costs, £*			
Total National Health Service	6683 (5632 to 8074)	4422 (3682 to 5291)	2261 (706 to 3589)
Admitted patient care	5168 (4271 to 6475)	3242 (2617 to 3924)	1926 (467 to 3128)
Outpatient	1186 (1045 to 1327)	949 (842 to 1066)	237 (50 to 414)
Concomitant medications	262 (168 to 385)	183 (125 to 252)	78 (–62 to 199)
General practitioner	93 (52 to 137)	103 (56 to 166)	–10 (–77 to 62)
Physiotherapy	38 (3 to 88)	18 (0 to 44)	19 (–35 to 62)
Emergency department	50 (10 to 100)	71 (26 to 128)	–20 (–94 to 50)
Observed health outcomes, EuroQol -5D-3L value set†			
Baseline utility	0·328 (0·259 to 0·392)	0·276 (0·188 to 0·366)	0·052 (–0·060 to 0·157)
54 week utility	0·718 (0·649 to 0·784)	0·659 (0·573 to 0·739)	0·059 (–0·051 to 0·165)
QALYs over 54 weeks	0·654 (0·588 to 0·709)	0·591 (0·518 to 0·658)	0·062 (–0·033 to 0·155)
Economic evaluation‡			
Costs	6919 (5503 to 8046)	4706 (3821 to 5516)	2212 (629 to 3677)
QALYs	0·616 (0·570 to 0·671)	0·559 (0·503 to 0·620)	0·057 (–0·009 to 0·124)
Incremental cost-effectiveness ratio	..	..	38 737

Data are mean (95% CI). TFESI=transforaminal epidural steroid injection. QALY=quality-adjusted life-year. *Admitted patient care, outpatient, and concomitant medications data considered complete. General practitioner, physiotherapy, and emergency department visits (patient-reported) subject to missing data. †Health outcomes for participants with observations at baseline and at weeks 18 and 54, adjusted for visit time deviations (n=55 for surgery group and n=48 for TFESI group). ‡Following imputation, regression analysis, and non-parametric bootstrapping.

Table 4: **Observed costs (£), health outcomes, and cost-effectiveness analysis results**

defined (ie, TFESI). Additionally, the chosen outcome instruments conformed to a recently defined core outcome dataset for low back pain.[29] Furthermore, as well as pain scores, functional assessments included ODQ and MRM (a sciatica-specific outcome), and an economic evaluation was included. The economic analysis has strengths in the use of routine patient-level NHS datasets and nationally reported costs, collected within a pragmatic, randomised controlled trial designed to reflect current management and NHS practice. Participant-reported health outcomes were reported using the EuroQol-5D-3L mapping algorithm, which is preferred by NICE. Deriving EuroQol-5D scores from the ODQ, this trial's primary outcome measure, was deemed unfeasible because no robust relationship exists between these measures.[30]

Limitations of the study include a degree of missing data and treatment crossover. It is possible that a difference of 10 points on the ODQ between the two treatments has been missed, given the 95% CIs found. However, the improvements in ODQ pain scores for the TFESI group were clinically significant in 43 (68%) of the 63 patients with complete and valid outcome data, and 47 (59%) of the 80 patients in the TFESI group did not have surgery during the trial. The effect of missing data was addressed with sensitivity analyses and the primary results were found to be robust. Regarding treatment crossover, previous studies have reported crossover rates of between 30% and 60% for non-surgical treatment groups. In this trial, only 13 (21%) of 63 patients in the TFESI group received surgery after they received TFESI and before the primary outcome assessment, which minimises primary outcome bias following intention-to-treat analysis. However, in total, 33 (41%) of the 80 patients in the TFESI group received surgery: 28 (35%) after receiving TFESI first, five (6%) received surgery only, and a further four (5%) received no treatment at all during the study period. Given that costs accrued were based on treatments received, this introduces potential implications for the cost-effectiveness estimates that would be observed in real-world practice.

The economic analysis had limitations, especially in relation to missing data for the postal questionnaires. Where possible, we employed assumptions around resource use, costs, and quality of life to maximise the use of acquired data; however, where this was not possible, we relied on multiple imputation.[31] Our estimation of productivity losses was included in a secondary analysis to reflect the high impact of sciatica on working days lost, but was subject to missing data and incomplete questionnaire reporting. Given that 65% recurrence rates of lower back pain after discectomy at 3 years have been reported,[32] applying a longer analytical time horizon might have provided insights into the longer-term estimate of cost-effectiveness. However, a modelled extrapolation would be liable to bias because participants of the NERVES trial were not followed up beyond 54 weeks.

Previous economic evaluations were found not to be generalisable to this analysis due to differences in setting, perspective, and interventions tested. A comparison between lumbar epidural steroid injection and placebo reported an incremental cost-effectiveness ratio of £44701 per QALY gained (provider perspective, which most closely reflects the NHS).[23] By contrast, NERVES used the preferable transforaminal route because the

injectate is much nearer to the site of pathology, the prolapsed disc, and involved nerve root.

The safety profiles of both treatments were different. Four patients in the surgery group required prolonged hospitalisation, revision surgery, or repair of meningocoele. One (1%) of the 105 patients who had surgery suffered a complete foot drop, despite a negative exploratory procedure within the first 24 h (no obvious cause for the nerve dysfunction could be identified). By contrast, no patients in the TFESI group suffered any serious adverse events.

For the first time, NERVES reports that use of TFESI as the initial invasive treatment is similarly effective to surgical microdiscectomy at reducing pain and disability from sciatica with symptom duration between 6 weeks and 12 months. Given the safety of TFESI, along with the unlikely cost-effectiveness of surgery as a first invasive treatment, we recommend that treating physicians strongly consider the use of TFESI as a stepwise invasive treatment for sciatica without neurological deficit of up to 12 months' duration. Surgery is still likely to be required for a considerable number of patients for whom TFESI might not be as effective.

Contributors

MJW developed the trial protocol in collaboration with GBu, EB, MS, DAH, and PRW. MJW oversaw the delivery of the trial, assisted in preparing trial update reports, and oversaw clinical aspects of the statistical analysis plan and clinical interpretation of the trial data. GBu proposed statistical analysis methods and approved the statistical analysis plan, and oversaw trial monitoring activities. GBa, CP, RM, PJH, and PRW contributed to trial design. DW, MS, SC, GBa, CP, RM, and PJH contributed to trial delivery. EB and HS contributed to all aspects of governance and trial delivery, and supported the preparation of progress reports. GBu, DAH, and PRW contributed to data capture methods. AB did the final statistical analysis under the supervision of GBu, with input from PRW. EW did the economic analysis under the supervision of DAH. DAH led and DH-M contributed to the economic evaluation. DAH and PRW contributed to development of the funding application. MJW led, and GBu and AB co-led the preparation of the final report. AB prepared data for reports, and data tables and figures for the final report. EW, DAH, EB, HS, and DH-M contributed to drafting the final report. EW, DAH, MS, and PRW contributed to editing the final report. EW, DAH, EB, HS, MS, SC, GBa, CP, RM, PJH, AM, and PRW contributed to reviewing the final report. MJW was chairperson of the Trial Management Group. AB, EW, GBu, EB, HS, DW, MS, SC, DAH, AM, and PRW were members of the TMG. AB, EW, DH, and GB were responsible for verifying the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AM reports grants from Union Chimique Belge Pharma, outside of the submitted work. PRW reports grants from the NIHR, outside of the submitted work. Liverpool Clinical Trials Centre is in receipt of the NIHR Clinical Trials Unit support funding. GBa reports grants and personal fees from Boston Scientific, Nevro Corporation, Abbott, and Nalu Medical, outside of the submitted work. PJH reports grants from the NIHR (Research Professorship) and the Royal College of Surgeons of England, outside of the submitted work. SC reports personal fees from Medtronic, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Fully anonymised data and a data dictionary will be available for data sharing from April 01, 2021. The trial protocol will also be made available. All requests for fully anonymised data should be sent to MJW. If access is granted, a contract between the sponsor or Liverpool Clinical Trials Centre and the external collaborator detailing the content, format, method of transfer, and recipient(s) must be fully executed prior to data transfer. Data transfer will occur via secure and confidential methods.

Acknowledgments

We acknowledge the support of the Supercomputing Wales project, which is part funded by the European Regional Development Fund via the Welsh Government.

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